Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias

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Supplemental data at www.neurology.org

ABSTRACT

Background: Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) MRI have high sensitivity and specificity for Creutzfeldt-Jakob disease (CJD). No studies, however, have demonstrated how MRI can distinguish CJD from nonprion causes of rapidly progressive dementia (npRPD). We sought to determine the diagnostic accuracy of MRI for CJD compared to a cohort of npRPD subjects.

Methods: Two neuroradiologists blinded to diagnosis assessed DWI and FLAIR images in 90 patients with npRPD (n = 29) or prion disease (sporadic CJD [sCJD], n = 48, or genetic prion disease [familial CJD, n = 6, and Gerstmann-Sträussler-Scheinker, n = 7]). Thirty-one gray matter regions per hemisphere were assessed for abnormal hyperintensities. The likelihood of CJD was assessed using our previously published criteria.

Results: Gray matter hyperintensities (DWI > FLAIR) were found in all sCJD cases, with certain regions preferentially involved, but never only in limbic regions, and rarely in the precentral gyrus. In all sCJD cases with basal ganglia or thalamic DWI hyperintensities, there was associated restricted diffusion (apparent diffusion coefficient [ADC] map). This restricted diffusion, however, was not seen in any npRPD cases, in whom isolated limbic hyperintensities (FLAIR > DWI) were common. One reader's sensitivity and specificity for sCJD was 94% and 100%, respectively, the other's was 92% and 72%. After consensus review, the readers' combined MRI sensitivity and specificity for sCJD was 96% and 93%, respectively. Familial CJD had overlapping MRI features with sCJD.

Conclusions: The pattern of FLAIR/DWI hyperintensity and restricted diffusion can differentiate sCJD from other RPDs with a high sensitivity and specificity. MRI with DWI and ADC should be included in sCJD diagnostic criteria. New sCJD MRI criteria are proposed.
Neurology® 2011;76:1711–1719

GLOSSARY

ADC = apparent diffusion coefficient; **CI** = confidence interval; **CJD** = Creutzfeldt-Jakob disease; **DWI** = diffusion-weighted imaging; **fCJD** = familial Creutzfeldt-Jakob disease; **FLAIR** = fluid-attenuated inversion recovery; **GSS** = Gerstmann-Sträussler-Scheinker; **npRPD** = nonprion causes of rapidly progressive dementia; **RPD** = rapidly progressive dementia; **sCJD** = sporadic Creutzfeldt-Jakob disease; **UCSF** = University of California, San Francisco.

Jakob-Creutzfeldt disease, more commonly known as Creutzfeldt-Jakob disease (CJD), typically presents as a rapidly progressive dementia (RPD), but other disorders can present in a similar fashion.[1] In more than one-third of suspected CJD cases seen at the University of California, San Francisco (UCSF) CJD clinical program, we found an alternative, nonprion, diagnosis.[1] Differentiating npRPD from CJD is critically important, both for infection control purposes and because many npRPDs are readily treatable. The EEG and CSF biomarkers have limited utility in CJD diagnosis.[2] Prior research has demonstrated that the MRI pattern of

e-Pub ahead of print on April 6, 2011, at www.neurology.org.

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Study funding: Supported by NIA/NIH grant R01 AG031189; K23 AG021989, grant P50 AG023501 from NIH National Institute on Aging; the California Alzheimer's Disease Centers (06–55318 DHS/ADP/ARCC); NIH/NCRR UCSF-CTSI grant number UL1 RR024131; the Michael J. Homer Family Fund (M.D.G.); the John Douglas French Foundation for Alzheimer's Research (M.D.G.); the McBean Foundation (M.D.G.); the Fondazione Tronchetti-Provera, Milan, Italy (P.V. and E.M.); and IRCCS, "C. Mondino" Foundation, the University of Pavia (E.C.).

Disclosure: Author disclosures are provided at the end of the article.

cortical and subcortical gray matter involvement has high sensitivity and specificity for CJD, but these studies did not use ideal npRPD controls.[2-4] We evaluated the sensitivity and specificity of fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) MRI for sCJD among a cohort of subjects with RPD and determined the MRI features that help to identify CJD.

METHODS **Subjects.** This retrospective study included 90 serial subjects, 61 with sporadic or genetic prion disease, and 29 with a nonprion RPD (npRPD) diagnosis, in whom CJD was considered (see figure e-1 on the *Neurology®* Web site at www.neurology.org for patient flow). Only subjects evaluated at the UCSF Memory & Aging Center between December 15, 2000, and February 15, 2007, with sufficient quality FLAIR and DWI MRI scans performed at our center were included (clinical and demographic data in table e-1). Subjects had extensive clinical evaluations, EEG, CSF, blood, and urine analyses. In many, total body CT was performed to rule out nonprion conditions. Most subjects had *PRNP* gene analysis (appendix e-1). Prion typing was done by the NPDPSC (Cleveland, OH). Criteria for diagnoses for the 61 patients with prion disease[5,6] and the 29 patients with npRPD[7-10] are shown respectively in tables e-1 and e-2, as well as appendix e-1.

Table 1 **UCSF 2005 and 2010 proposal of MRI criteria for CJD diagnosis**

Diagnosis	UCSF 2005 criteria[3]	UCSF 2011 proposed modifications/additions
MRI definitely CJD	FLAIR and DWI (or DWI alone) hyperintensity in:	DWI > FLAIR hyperintensity in:
	1. Cortex (>1 gyrus) and striatum	Classic pathognomonic: cingulate, striatum, and >1 neocortical gyrus (often precuneus, angular, superior, or middle frontal gyrus) Supportive for subcortical involvement: • Striatum with anterior-posterior gradient • Subcortical ADC hypointensity Supportive for cortical involvement: • Asymmetric involvement of midline neocortex or cingulate • Sparing of the precentral gyrus • ADC cortical ribboning hypointensity
	2. Cortex only (>3 gyri)	Cortex only (>3 gyri); see supportive for cortex (above)
MRI probably CJD	1. Unilateral striatum or cortex ≤3 gyri	Unilateral striatum or cortex ≤3 gyri; see supportive for subcortical (above); see supportive for cortex (above)
	2. Bilateral striatum or posteromesial thalamus	Bilateral striatum or posteromesial thalamus; see supportive for subcortical (above)
	3. FLAIR > DWI hyperintensities	Moved to probably not CJD (see below)
MRI probably not CJD	1. Only FLAIR/DWI abnormalities in limbic areas, where hyperintensity can be normal (insula, cingulate)	Only FLAIR/DWI abnormalities in limbic areas, where hyperintensity can be normal (e.g., insula, anterior cingulate, hippocampi) and ADC map does not show restricted diffusion in these areas
	2. DWI hyperintensities due to artifact (signal distortion)	DWI hyperintensities due to artifact (signal distortion); see other MRI issues (below)
	3. FLAIR > DWI hyperintensities	FLAIR > DWI hyperintensities; see other MRI issues (below)
MRI definitely not CJD	1. Normal	No change from prior criteria
	2. Abnormalities not consistent with CJD	No change from prior criteria
Other MRI issues	In prolonged courses of sCJD (~>1 year) brain MRI might show significant atrophy with loss of DWI hyperintensity, particularly in areas previously with restricted diffusion	
	To help distinguish abnormality from artifact, obtain sequences in multiple directions (e.g., axial and coronal)	

Abbreviations: ADC = apparent diffusion coefficient; CJD = Creutzfeldt-Jakob disease; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; sCJD = sporadic Creutzfeldt-Jakob disease; UCSF = University of California, San Francisco.

Standard protocol approvals, registrations, and patient consents. We received approval from our institutional internal review board for conducting this study.

MRI acquisition. Brain MRIs were performed on 2 GE Signa 1.5-T scanners at our center. FLAIR and DWI/DTI in axial planes (slice thickness range: 3–5 mm) were obtained for all patients, and most had FLAIR and DWI in coronal planes. Only the DWI combined image, the average of the multiple diffusion directions, was reviewed. See appendix e-1 for additional details.

MRI visual assessment. Two neuroradiologists (reader 1, 4 years experience; reader 2, 20 years experience), blinded to the clinical diagnosis, independently reviewed all MRI sequences from the first UCSF scan. To differentiate true abnormalities from FLAIR hyperintensities due to the normal variations of T2 signal and DWI artifact,[3] images were viewed in both axial and coronal planes using MRIcro software (www.mricro.com).

The gray matter involvement on FLAIR and DWI images was reported according to 26 cortical and 5 subcortical subdivisions per hemisphere, using minor modifications of the Tzourio-Mazoyer atlas (appendix e-1).[11] Based on FLAIR and DWI , each reader classified subjects as definitely, probably, probably not, or definitely not CJD, according to our prior MRI criteria (table 1).[3] Apparent diffusion coefficient (ADC) maps were reviewed only if subcortical gray matter DWI abnormalities were found, as ADC hypointense signal in the cortex is usually difficult to detect by visual assessment.[12]

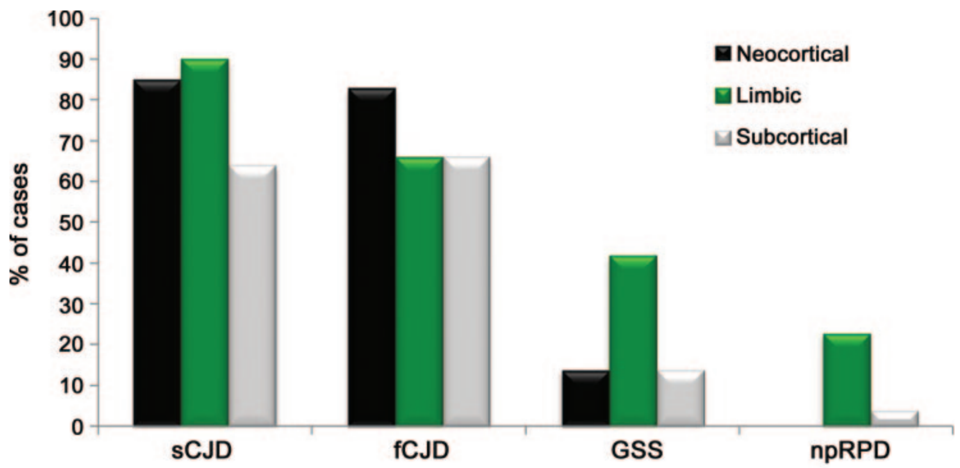
Consensus review. If readers disagreed on a diagnosis, they re-examined the MRI together and made a consensus diagnosis. At this time, readers also noted whether FLAIR or DWI hyperintensities were brighter. Sensitivity, specificity, and 95% confidence intervals were calculated for individual and consensus ratings (SAS, version 9.2, SAS Institute, Cary, NC).

Determining patterns of gray matter involvement in sCJD. Each of 31 hemispheric regions on DWI MRI was scored 0, 1, or 2, according to how many readers judged a region as hyperintense. The percentage of subjects with sCJD with involvement of each brain region was determined by averaging the ratings of both readers. Next, subjects with sCJD were categorized into 6 different patterns of gray matter involvement (table e-3).

Unblinded review and identifying differentiating features. After consensus review, the readers re-examined the MRIs "unblinded" to identify crucial differentiating features. Finally, we modified our sCJD MRI criteria[3] based on the results of this analysis, as well as our clinical experience since completing this analysis.

RESULTS **Sensitivity and specificity of the visual assessment for sCJD.** Sensitivity and specificity for sCJD (vs npRPD) were higher for reader 2 (sensitivity 94%, 95% confidence interval [CI] 0.83–0.99;

Figure 1 Frequency of gray matter fluid-attenuated inversion recovery (FLAIR) or diffusion-weighted imaging (DWI) hyperintensities in different disease cohorts



No subject with nonprion causes of rapidly progressive dementia (npRPD) had any neocortical hyperintensity, but about 25% had predominantly limbic involvement. Almost half of Gerstmann-Sträussler-Scheinker (GSS) cases were believed to have DWI or FLAIR limbic hyperintensity. Predominant limbic hyperintensity is therefore not suggestive of sporadic Creutzfeldt-Jakob disease (sCJD), but possibly of GSS or npRPD. Familial CJD (fCJD) has an overlapping pattern of MRI abnormality with sCJD.

specificity 100%, 95% CI 0.88–1.00) than reader 1 (sensitivity 92%, 95% CI 0.80–0.98; specificity 72%, 95% CI 0.52–0.87). A consensus diagnosis was reached on all but 3 cases (1 sCJD, 2 npRPD); by conservatively classifying these cases as misreads, consensus sensitivity was 96% (95% CI 0.86–1.00) and specificity was 93% (95% CI 0.77–0.99) using our criteria.[3]

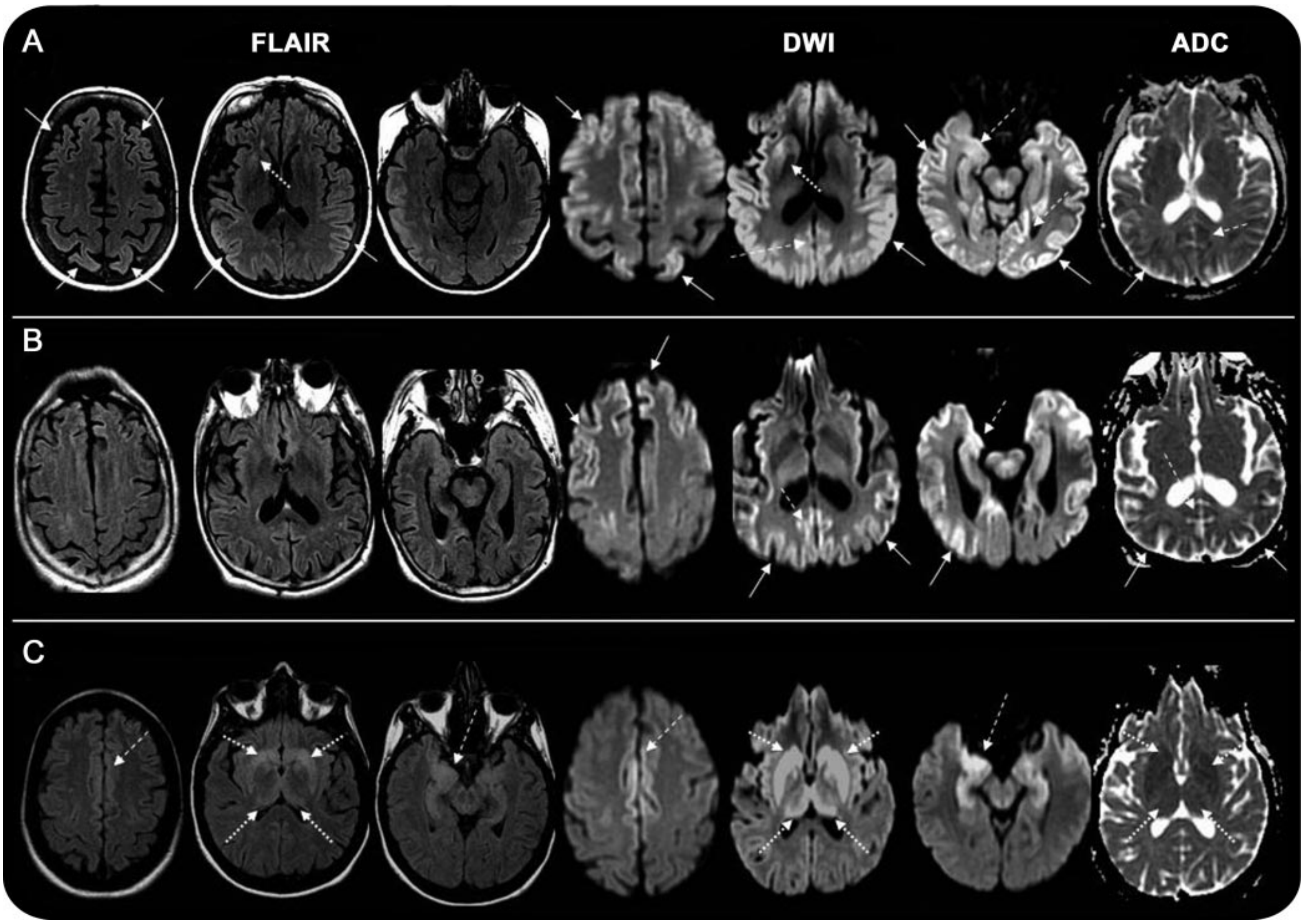
Pattern of FLAIR and DWI neocortical, limbic, and subcortical hyperintensities in sCJD vs npRPD. The region of gray matter involvement was different between the sCJD and npRPD patient groups (figure 1). All but one (see below) patient with sCJD had gray matter hyperintensities in the neocortical, limbic, or subcortical areas—or in combinations of these areas—but none had hyperintensity in limbic areas alone (table e-3). Gray matter abnormalities in sCJD were always more evident on DWI than FLAIR and in some cases noted only on DWI. The common patterns in sCJD were neocortical, limbic, and subcortical (54%) and neocortical and limbic (27%) (figure 2, table e-3). No clear MRI pattern was noted based on molecular classification of sCJD by codon 129 polymorphism or prion type.[13] There was no neocortical involvement in 11% percent of sCJD cases, including both VV2 cases, and the single MM2-thalamic case did not show gray matter abnormalities, consistent with other studies.[13,14]

Only 9 of 29 patients with npRPD (23%) had abnormal gray matter hyperintensities; all were greater on FLAIR than on DWI. All had limbic involvement. Two also had subcortical hyperintensities. Seven with isolated limbic involvement had autoimmune diagnoses (figures 1 and 3). To determine whether subcortical DWI hyperintensities were related to restricted diffusion or T2 shine-through, readers examined the ADC maps during the blinded assessment. Subcortical regions with DWI hyperintensity had normal intensity on the ADC map in patients with npRPD (T2 shine-through), but were always hypointense (restricted diffusion) on the ADC map in sCJD.

MRI features in genetic prion disease. Patterns and frequencies of DWI and FLAIR hyperintensities differed between patients with familial CJD (fCJD) and patients with Gerstmann-Sträussler-Scheinker (GSS) (figures 1 and 3). Five of 6 fCJD MRIs had gray matter hyperintensities and were read as positive; 4 (3 E200K and 1 D178N codon 129VV) had diffuse (neocortical, limbic, and subcortical) involvement, and 1 (V180I) had only neocortical hyperintensities. The sixth subject with fCJD (5-octapeptide repeat) had no hyperintensities. Of 7 GSS MRIs, only one was read positive (F198S), with cortical ribboning (neocortex, limbic, and striatum) on DWI. Two (A117V and another F198S) had only limbic hyperintensities, on both FLAIR and DWI. The remaining 4 (P102L and 3 A117V) had no gray matter abnormalities.

Detailed analysis of the pattern of FLAIR and DWI hyperintensities at the gyral-nuclear level in patients with sCJD. Because neocortical hyperintensities were found in only a few npRPD cases, the percentage of gray matter involvement at detailed anatomic levels

Figure 2 Three common variations of sporadic Creutzfeldt-Jakob disease presentation on MRI



(A) Neocortical (solid arrow), limbic (dashed arrow), and subcortical gray matter (dotted arrow). (B) Neocortical and limbic cortex. (C) Limbic and subcortical. Note that the diffusion-weighted imaging (DWI) shows the hyperintensities much more than the corresponding fluid-attenuated inversion recovery (FLAIR) sequences, and that DWI hyperintensities often have corresponding apparent diffusion coefficient (ADC) hypointensity. Pattern A was found in 54% of cases, pattern B in 27% of cases, and pattern C in 9% of cases. Note that the abnormalities are more readily seen on DWI than on FLAIR. ADC hypointensity, indicating restricted diffusion, corresponds to most DWI hyperintensities. ADC abnormalities are most easily identified in the basal ganglia.

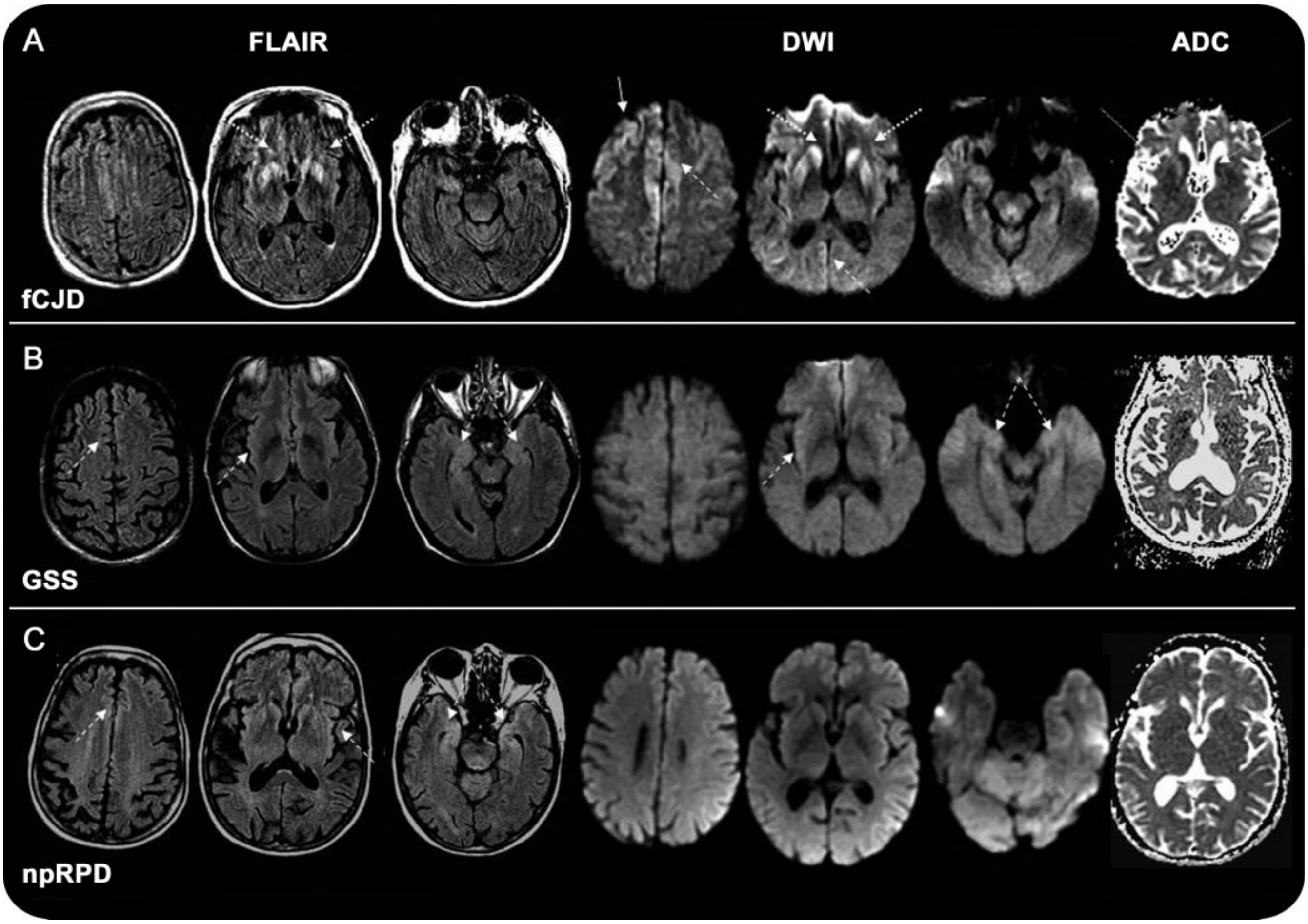
(31 areas per hemisphere) was calculated only in the sCJD group. DWI and, to a lesser extent, FLAIR hyperintensities in the cingulate, precuneus, angular, parahippocampal, superior and middle frontal gyri, and caudate were present in more than 50% of sCJD cases (figure 4). Asymmetric involvement was found in the majority of sCJD cases and was especially notable in the mesial cortex and cingulate (figure 2). Hemispheres were equally involved in the lateral frontal lobe and subcortical structures, but the left hemisphere was more frequently involved in parietal, temporal, and occipital lobes. There was relative sparing of the precentral gyrus, with DWI hyperintensity in only 3 patients (6%).

In sCJD (and fCJD), striatal hyperintensity almost always revealed a gradual anterior-posterior gradient, involving mainly the caudate (more than 50% of cases) with relative sparing of the posterior putamen (figure 2). The posterior putamen, however, also was very hyperintense in some patients with predominantly subcortical involvement. ADC hypointensity was often seen in the pallidus of the predominantly subcortical sCJD cases, but there was concomitant DWI hyperintensity in only one case (figure 2C).

Thalamic DWI involvement was usually bilateral, involving the dorsomedian and posterior (pulvinar) regions, and often coupled with bilateral striatal involvement. This pattern is similar to but less intense than the "double hockey stick" sign pattern seen in many variant CJD cases.[15] Interestingly, when the double hockey stick sign was seen on DWI, the ADC maps showed more diffuse thalamic hypointensity. The more specific MRI feature for vCJD, the pulvinar sign (posterior thalamus brighter than anterior putamen),[15] was not seen in any study subjects.

MRI review after "unblinding." Unblinded review of all cases showed the diagnostic value of the ADC

Figure 3 Axial MRI from representative cases of familial Creutzfeldt-Jakob disease (fCJD) (A), Gerstmann-Sträussler-Scheinker (GSS) (B), and nonprion causes of rapidly progressive dementia (npRPD) (C)



(A) A fCJD case (E200K mutation) showing neocortical (solid arrow) involvement more evident in the right hemisphere, especially in the right frontal lobe, limbic involvement (dashed arrow) more evident in the right anterior cingulate and right insula and subcortical (dotted arrow) hyperintensities, greater in diffusion-weighted imaging (DWI) than in fluid-attenuated inversion recovery (FLAIR) images. Note the subcortical apparent diffusion coefficient (ADC) hypointensity in bilateral striatum. The image was read as Creutzfeldt-Jakob disease (CJD). (B) A GSS case (F198S mutation) with bilateral limbic hyperintensity in the anterior cingulate, insula, and subtle involvement in the mesiotemporal cortex, equally evident in DWI and FLAIR images. Image read as not CJD. (C) An npRPD case with limbic encephalopathy due to anti-AMPAR with anti-Sox2 antibodies and small-cell lung cancer. Note significant bilateral hyperintensity in mesiotemporal cortex (including hippocampus and amygdala), insula, and cingulate, greater on FLAIR than on DWI images. Image read as not CJD.

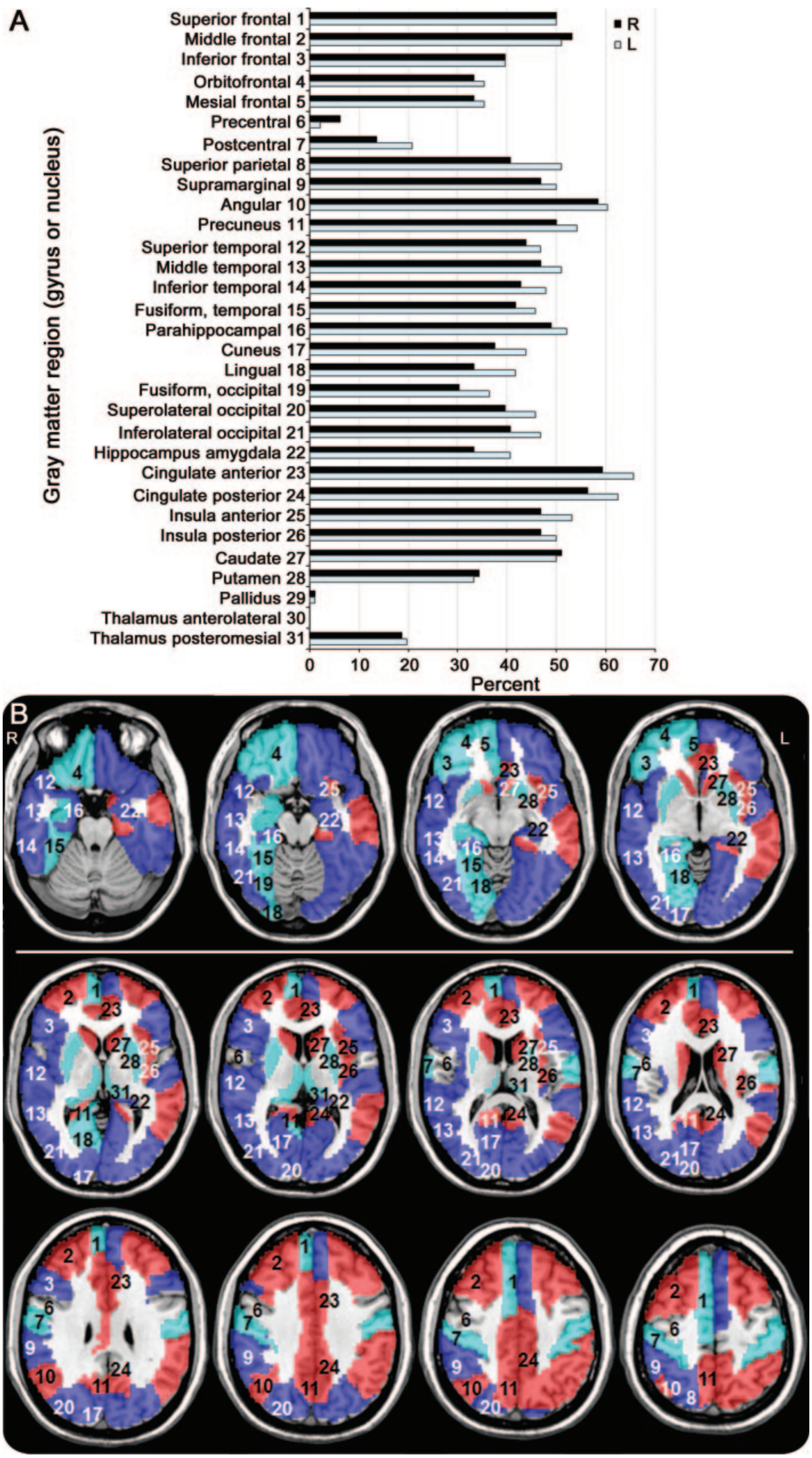
map in the subcortical regions. Furthermore, failure to notice diffuse hyperintense cortical signals in subjects without subcortical abnormalities caused false-negative readings. False-positive ratings were usually due to misinterpreting artifactual hyperintense signals on DWI as restricted diffusion, particularly on poor-quality scans.

Three cases without consensus MRI diagnosis at consensus review. In 2 cases, the cortical DWI and FLAIR abnormalities in the caudate head, anterior cingulate, and insula were slight. The third case had FLAIR abnormalities in the cerebellar peduncles, unilateral caudate head, and DWI abnormalities in these areas and the cortex. At unblinding, the first case was probable DLB, the second pathology-proven sCJD, and the third pathology-proven sarcoid. In the DLB and sarcoid cases, the caudate was normo-intense on the ADC map. In the sCJD case, the caudate was slightly hypointense on the ADC map, and DWI cortical ribboning in the frontal cortex was so subtle it was missed by readers at initial reading.

Improving MRI criteria for sCJD. Based on the above review and the authors' collective experience with prion and npRPD cases, we modified our MRI criteria[3] for sCJD (table 1). When these were reapplied to the sCJD and npRPD MRIs, unblinded consensus review found 98% sensitivity (95% CI 0.89–1.00) and 100% specificity (95% CI 0.88–1.00).

DISCUSSION In this study, we show that the pattern of MRI involvement can differentiate sCJD

Figure 4 **Frequency of gray matter hyperintensities at gyral and nuclear level in sporadic Creutzfeldt-Jakob disease (sCJD)**



(A) Percent of subjects with sCJD with DWI brighter than FLAIR in each of 31 brain regions per right (black) and left (blue) hemisphere. (B) Color-coded overlay of frequency of MRI involvement in 31 brain regions per hemisphere. Light blue represents areas involved in 10%–35% of cases, dark blue 35%–50%, red 50%–65%. Neocortical regions are indicated with numbers (1–21) in the right hemisphere; limbic (22–26) and subcortical (27–31) regions are indicated in the left hemisphere.

from npRPD. Using FLAIR and DWI MRI, we found that after consensus review, MRI sensitivity and specificity for sCJD were 98% and 93%, respectively, higher than any other diagnostic test.[4,16-18] We identified 4 distinguishing MRI features:

1. In sCJD, hyperintensity on DWI was greater than on FLAIR, but in npRPD, hyperintensity on FLAIR was greater than on DWI.
2. In subjects with sCJD with subcortical DWI hyperintensity, ADC in these regions was always hypointense (i.e., restricted diffusion).
3. Isolated limbic involvement was not found in sCJD, but often seen in npRPD.
4. sCJD has characteristic DWI patterns of gray matter involvement.

Regarding the first 2 features, the prevalence of DWI over FLAIR hyperintensities suggests diffusion restriction is a crucial feature of MRI in sCJD; diffusion restriction and T2 prolongation both contribute to DWI hyperintensity, but only T2 prolongation causes FLAIR hyperintensity. Only sCJD cases had ADC hypointensity correlating with DWI subcortical hyperintensity and this finding had high specificity for sCJD. The diffusion restriction is probably related to vacuolation.[19] This study used the first MRI scan obtained at our institution, but we and others have observed that diffusion restriction might decline in late stages of sCJD, particularly in patients with very prolonged courses and significant atrophy.[20,21] Nevertheless, we believe that the prevalence of DWI over T2 abnormalities is one of the most important MRI criteria for diagnosing sCJD, which is supported by other studies.[18,21] Furthermore, DWI is often bright very early in CJD when T2-weighted images are not.[20,21]

Many studies have confirmed the sensitivity of DWI in sCJD, some gPrDs, and vCJD.[3,13,18,21] In this study we show the high specificity of diffusion restriction (with DWI and ADC map) in the basal ganglia in sCJD compared to npRPDs. A recent large study examined the sensitivity and specificity of FLAIR, and in some cases DWI, MRI in sCJD compared to subjects initially suspected of CJD, but in whom other diagnoses were found.[18] This article proposed new MRI criteria for sCJD, but had several problems. First, the authors did not look at true diffusion restriction (ADC map), which is critical for differentiating CJD from npRPD. Secondly, they do not include cingulate, hippocampal, insular, and frontal cortical involvement because of a high rate of false-positive FLAIR or DWI MRI readings in these regions. These regions, however, are among the most common areas affected in CJD (figure 1) and false positivity due to artifact can be avoided by performing sequences in multiple planes and examining for restricted diffusion (ADC map).

Other npRPD conditions (many of which were not included in this cohort) might present with subcortical or cortical DWI hyperintensity—sometimes with decreased ADC—and might mimic CJD MRI findings. For example, subcortical diffusion restriction can be found in striatum in extrapontine myelinolysis[22] and Wilson disease,[23] and in the posteromesial thalamus in Wernicke encephalopathy[24] and in *Bartonella* infection.[25] Since our study was completed, we have identified 2 patients with npRPD (hyperglycemia with seizures and extrapontine myelinolysis) with some MRI findings overlapping those of CJD, DWI hyperintensity, and ADC hypointensity in the striatum (manuscript in preparation). A few npRPDs, such as anti-CV2 limbic encephalopathy and neurofilament inclusion body disease, have striatal T2/FLAIR hyperintensity similar to CJD; in these conditions, however, DWI/ADC abnormalities are absent. Cortical diffusion restriction can be seen in the acute phase of viral encephalitis[26] and focal epileptic status.[27] Importantly, status epilepticus occurs in npRPDs, such as limbic encephalopathy, and might mimic CJD clinically.[28] "Strategic" stroke dementia can show cortical hyperintensity.[29] Acute viral encephalitis, focal epileptic status, and stroke usually present cortical swelling, subcortical abnormalities, and often contrast enhancement.[26,27] Although DWI and ADC are the most important sequences for diagnosing sCJD, FLAIR images and, in selected cases, T1 pre- and postcontrast must be carefully evaluated in all patients with rapidly progressive dementia. These conditions must be considered when evaluating a patient with suspected CJD.

Isolated limbic involvement might help distinguish sCJD from npRPD, for it was found only in our npRPD group, typically in autoimmune encephalopathy. To our knowledge, ADC decreases have never been reported in these encephalopathies, but this might occur with seizures, although this should disappear after seizures have been controlled. If isolated limbic hyperintensity is greater on FLAIR than DWI, we suggest that this be a criterion for "probably not CJD." If isolated limbic hyperintensity is greater on DWI, particularly with accompanying ADC hypointensity, encephalitis and seizures should be considered.

Another distinguishing feature of sCJD was its pattern of gray matter involvement. Consistent with prior studies,[3,4] we found that hyperintensities were more commonly cortical than subcortical (table e-3). We also identified the same most frequently involved cortical regions as another study,[30] except we rarely found occipital cortical involvement. Although the highest frequencies of any specific area of gray matter involvement in that study were significantly higher than in our cohort (85%–95% compared to 50%–65%), 13 cases were studied without DWI images and no control group was included. As they knew all cases were CJD, they might have overestimated hyperintensities, possibly explaining the more frequent involvement of the precentral gyrus in their study (40%) compared to ours (5%), and why parahippocampal hyperintensities, involved in 50% of our sCJD cohort, were not reported. Susceptibility artifacts make evaluating the anterior parahippocampal gyrus difficult, but the posterior portion can be evaluated more reliably. Thus, to help determine if the abnormal intensities are real or artifact, we recommend performing (or at least reviewing) the DWI/ADC sequences in 2 planes, axial and coronal.

The areas with less frequent FLAIR/DWI hyperintensity in sCJD were the pallidus and precentral gyrus. This characteristic "precentral sparing" sign was especially notable in subjects with sCJD and subjects with fCJD with diffuse cortical involvement (figure 2). Although motor deficits are common in CJD, the sparing of the motor strip might reflect the absence of frank paralysis in most patients. Conversely, because precentral gyrus and the pallidus accumulate the most age-related iron, they have the most hypointense T2-weighted signal.[31,32] Although the pallidus can be relatively spared on DWI in sCJD,[33] pallidal T1 hyperintensity might be pathologically associated with high levels of prion deposits.[34] We suspect that involvement of pallidus and precentral gyrus is underestimated on FLAIR and DWI sequences because the concurrent iron-related hypointensity masks the hyperintense signal from prion disease. This "T2 blackout" effect is significant in FLAIR, T2-weighted, and probably greater in echoplanar DWI images.[35] One sCJD study demonstrated ADC decrease, despite normal DWI, in the precentral gyrus.[36] Of note, our sCJD MM2-thalamic case had a normal MRI, consistent with most cases in the literature.[37]

The MRI pattern in our patients with fCJD generally resembled those of sCJD, but in most GSS cases this pattern was not found. As subcortical ADC maps were examined only in cases with DWI subcortical hyperintensity, after the study, we noted subcortical ADC hypointensity without DWI hyperintensity in some GSS cases; this may be due to the "T2 blackout" effect. Although the P102L case did not have typical sCJD MRI findings, and nor have subsequent cases seen at our center, at least one case has been reported to have a classic CJD MRI.[38]

As we found variability among readers, it seems clear that accurate interpretation of MRIs in subjects with CJD requires knowledge of the findings and experience with CJD. Our new criteria should improve diagnostic accuracy and reduce this variability. It is paramount that neurologists and radiologists familiarize themselves with these findings. Future studies should address issues of inter- and intrarater reliability and also might use postprocessing methods to accurately quantitate mean diffusivity values (ADC map).

The patterns of FLAIR and DWI abnormalities can differentiate sCJD from npRPD with high accuracy, whereas only some genetic prion cases have overlapping MRI features with sCJD. We propose modification of our prior sCJD MRI (table 1) criteria to improve the sensitivity and specificity of the MRI findings, based on the anatomic distribution of DWI-FLAIR hyperintensities, the relative DWI to FLAIR signal, and the ADC map in subcortical areas. MRI with DWI and ADC should be included in sCJD diagnostic criteria.

ACKNOWLEDGMENT

The authors thank Alan Bostrom, MS, for statistical assistance.

DISCLOSURE

Dr. Vitali has received research support from the Fondazione Tronchetti-Provera, Milan, Italy. Dr. Maccagnano and Dr. Caverzasi report no disclosures. Dr. Henry serves as an Associate Editor for *Frontiers in Neuroscience* and receives research support from the NIH (NINDS, NIBIB, NCI) and the Lupus Research Institute. Dr. Haman, C. Torres-Chae, and D.Y. Johnson report no disclosures. Dr. Miller serves on a scientific advisory board for the Alzheimer's Disease Clinical Study, serves as an Editor for *Neurocase*, and served as an Associate Editor of ADAD; receives royalties from the publication of *Behavioral Neurology of Dementia* (Cambridge, 2009), *Handbook of Neurology* (Elsevier, 2009), and *The Human Frontal Lobes* (Guilford, 2008); serves as a consultant for Lundbeck Inc., Allon Therapeutics, Inc., Novartis, and TauRx Pharmaceuticals; serves on the Board of Directors for the John Douglas French Foundation for Alzheimer's Research and for The Larry L. Hillblom Foundation; and receives research support from Novartis, the NIH/NIA, and the State of California Alzheimer's Center. Dr. Geschwind serves on a scientific advisory board for Lundbeck Inc.; serves on the editorial board of *Dementia and Behavior*; has served as a consultant for MedaCorp Inc, Gerson-Lehman Group, and The Council of Advisors; has served on speakers' bureaus for Forest Laboratories, Inc., Pfizer Inc, Novartis, and Lundbeck Inc.; and received research support from the NIH/NIA, the Michael J. Homer Family Fund, the John Douglas French Foundation for Alzheimer's Research, and the McBean Foundation.

Received July 26, 2010. Accepted in final form February 10, 2011.

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